PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P36258WO/NCB	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IB2004/003804	International filing date *(day/month/year)* 04.11.2004	Priority date *(day/month/year)* 14.11.2003
International Patent Classification (IPC) or national classification and IPC INV. A61K9/00		
Applicant JAGOTEC AG et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.06.2005	20.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Ventura Amat, A Telephone No. +31 70 340-3562

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/003804

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-24 as originally filed

   Claims, Numbers

   1-11 received on 15.09.2005 with letter of 13.09.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8-10
	No:	Claims	1-7,11
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V.

1 The following documents are referred to in this communication:
D1 : WO 01/78693 A (CHIESI FARMACEUTICI) 25 October 2001 (2001-10-25)
D2 : US 6528096 (ROSELLA MUSA ET AL.) 4 March 2003 (2003-03-04)
D3 : WO 00/28979 A (SKYEPHARMA AG) 25 May 2000 (2000-05-25)
D3A: US 6645466 B1 (MANFRED KELLER; ET AL.) 11 November 2003 (2003-11-11)

2 NOVELTY

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1-7,11 is not new in the sense of Article 33(2) PCT.

Independent claim 1 describes a dry powder for inhalation comprising drug particles and carrier particles, further containing magnesium stearate particles in an amount of at least 0.5% by weight of the formulation disposed on the surface of the carrier such that the surface coverage of the carrier particles is less than 10%. It is understood that the range of surface coverage is between 0% (no surface coverage) and 10%.

Document D1 discloses (claims 1,2,4,6,9; page 11, lines 3-8) a powder for dry powder inhalers comprising a mixture of a drug and granules comprising an excipient and 1 to 10% by weight of magnesium stearate where a degree of coating of at least 5% is achieved. The feature that the carrier is partially coated with less than 10% of magnesium stearate as claimed in claim 1 of the Application is indeed disclosed in D1, the fact that the excipient (which is the same compound as the carrier, differing only in its particle size) is also coated is irrelevant. This is relevant for claims 1-7 and 11.

Claims 8-10 are considered novel.

3 INVENTIVE STEP

3.1 CLAIM 8

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 8 does not involve an inventive step in the sense of Article 33(3) PCT.

Document D3A is regarded as being the closest prior art to the subject-matter of the present Application: A method to obtain a dry powder inhaler which exhibits a high fine particle fraction by blending in a tumble mixer particles of inactive carrier and magnesium stearate in an amount between 0.1 and 2% that adhere to said carrier and further adding an active compound (claim 1; column 3, line 60 to column 4, line 25; column 7, lines 54-67; column 8 lines 46-62; examples 1,3-6). This method solves the same problem.

The difference with claim 8 is that D3 does not disclose how long is the mixing time and, thus, to what extent magnesium stearate adheres to the carrier particles.

The technical effect of the difference is unknown.

The problem is now to find an alternative method of making a dry powder inhaler comprising the desired particles.

The skilled person would select the appropriate mixing time to improve the fine particle fraction to obtain the desired particles.

Claim 8 is, thus, not inventive.

3.2 CLAIM 10

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 10 does not involve an inventive step in the sense of Article 33(3) PCT.

Document D3A is regarded as being the closest prior art to the subject-matter of

the present Application: A method to obtain a dry powder inhaler by blending in a tumble mixer particles of inactive carrier and magnesium stearate in an amount between 0.1 and 2% that adhere to said carrier and further mixing an active compound (claim 1; column 3, line 60 to column 4, line 25; column 7, lines 54-67; column 8 lines 46-62; examples 1,3-6). This method solves the same problem.

The difference with claim 10 is that D3 does not disclose how long the mixing time of carrier and magnesium stearate nor the mixing time for the active and the previously obtained blend are.

The technical effect of the difference is unknown.

The problem is now to find an alternative method of making a dry powder inhaler.

The skilled person would select the appropriate mixing times to obtain the desired dry powder inhalers.

Claim 10 is, thus, not inventive.

CLAIMS

1. A dry powder for inhalation comprising active particles and carrier particles for supporting active particles, the formulation further containing magnesium stearate in an amount of at least 0.5% by weight of the formulation, and wherein particles of magnesium stearate are disposed on the surface of the carrier particles such that the surface coverage of carrier particles is less than 10%.

2. A dry powder according to claim 1 wherein the surface coverage of carrier particles is from 1 to 5%.

3. A dry powder according to claim 1 or claim 2 wherein the magnesium stearate is present in amounts of 0.5 to 2% by weight.

4. A dry powder according to any of the preceding claims wherein the magnesium stearate is present in amounts of form 0.6 to 1% by weight.

5. A dry powder according to any of the preceding claims wherein the active substance is selected from beta-mimetics selected from Levalbuterol, Terbutalin, Reproterol, Salbutamol, Salmeterol, Formoterol, Fenoterol, Clenbuterol, Bambuterol, Tulobuterol, Broxaterol, Epinephrin, Isoprenaline or Hexoprenaline; Anticholinergic selected from Tiotropium, Ipratropium, Oxitropium or Glycopyrronium; Corticosteroids, selected from Butixocart, Rofleponide, Budesonide, Ciclosenide, Mometasone, Fluticasone, Beclomethasone, Loteprednol or Triamcinolone; Leukotrienantagonists, selected from Andolast, Iralukast, Pranlukast, Imitrodast, Seratrodast, Zileuton, Zafirlukast or Montelukast; Phosphodiesterase-Inhibitors, selected from Filaminast or Piclamilast; PAF-Inhibitors, selected from Apafant, Forapafant or Israpafant; potassium channel opener selected from Amiloride or Furosemide; analgesics (pain killers) selected from Morphine, Fentanyl, Pentazocine, Buprenorphine, Pethidine, Tilidine, Methadone or Heroin; potency agents selected from Sildenafil, Alprostadil or Phentolamine; pharmaceutically acceptable derivative or salt of any of the foregoing compounds or classes of compounds; and

macromolecules selected from proteins, peptides, oligopeptides, polypeptides, polyamino acids, nucleic acids, polynucleotides, oligo-nucleotides and high molecular weight polysaccharides.

6. A dry powder according to any of the preceding claims wherein the carrier material is selected from a mono- or di-saccharides such as glucose, lactose, lactose mono-hydrate, sucrose or trehalose; sugar alcohols such as mannitol or xylitol; polylactic acid; or mixtures thereof.

7. A dry powder according to any of the preceding claims wherein the carrier is lactose mono-hydrate.

8. A method of making a dry powder for inhalation as claimed in any one of claims 1 to 7 comprising the step of blending magnesium stearate with a carrier material in a diffusion blender for a period of less than 30 minutes.

9. A method of making a dry powder for inhalation as claimed in claim 8 consisting of the consecutive steps of:-

(i) magnesium stearate with a carrier material in a diffusion blender for a period of less than 30 minutes,

(ii) blending the mixture of step (i) with an active substance in a diffusion blender for a period of less than 30 minutes.

10. A method of making a dry powder consisting of the consecutive steps of:

(i) magnesium stearate with a carrier material in a diffusion blender for a period of less than 30 minutes;

(ii) blending the mixture of step (i) with an active substance in a diffusion blender for a period of less than 30 minutes.

11. A multi-dose dry powder inhaler containing a formulation as defined in any of the claims 1 to 7.